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**Patentanmeldung Nr. Patent application No. Demande de brevet n°**

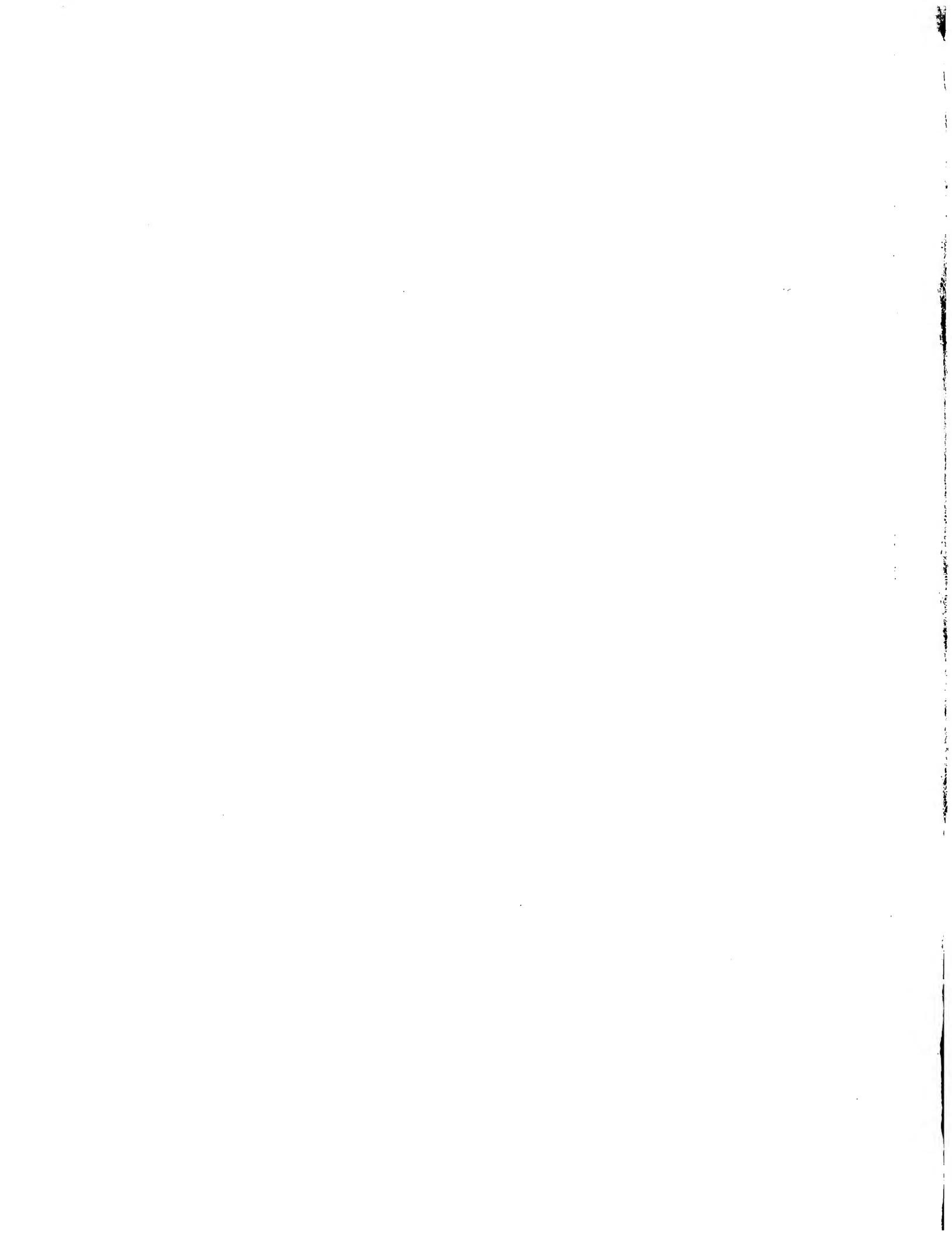
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Der Präsident des Europäischen Patentamts;  
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets  
p.o.

**R C van Dijk**





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Demande no:

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Anmelder/Applicant(s)/Demandeur(s):

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ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.  
If no title is shown please refer to the description.  
Si aucun titre n'est indiqué se referer à la description.)

Pharmaceutical composition of antiviral agents

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Boehringer Ingelheim International GmbH  
55216 Ingelheim

Case 1-1475  
PriorText

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## PHARMACEUTICAL COMPOSITION OF ANTIVIRAL AGENTS

### FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition  
5 useful for the treatment of viral infections comprising  
tipranavir and at least one antiviral active compound of  
formula (I). Furthermore the present invention relates to a  
use of tipranavir in combination or alternation with a  
compound of formula (I) in the prophylaxis or treatment of a  
10 viral infection in a patient. The present invention also  
relates to a use of tipranavir in combination with a compound  
of formula (I) for the manufacture of a medicament for the  
prophylaxis or treatment of a viral infection in a patient. In  
addition the present invention relates to a kit of parts and  
15 to a manufacture for the prophylaxis or treatment of a viral  
infection in a patient.

### BACKGROUND OF THE INVENTION

20 Human immunodeficiency virus (HIV) is recognized as the  
causative agent in AIDS.

Current therapies for HIV infection focus on inhibiting the  
activity of viral enzymes which are essential to the life  
25 cycle of the virus. The agents that are presently in use fall  
mainly into three classes; designated Nucleoside Reverse  
Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse  
Transcriptase Inhibitors (NNRTIs), and Protease Inhibitors  
(PIs). Presently, combination therapies, i.e. the selection of  
30 two or more antiretroviral agents taken together to make up a  
"drug cocktail," are the preferred treatment for HIV  
infection. Combination therapies have been shown to reduce the  
incidence of opportunistic infections and to increase survival

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time. Typically, the drug cocktail combines drugs from different classes, so as to attack the virus at several stages in the replication process. This approach has been shown to reduce the likelihood of the development of virus forms that 5 are resistant to a given drug or class of drugs.

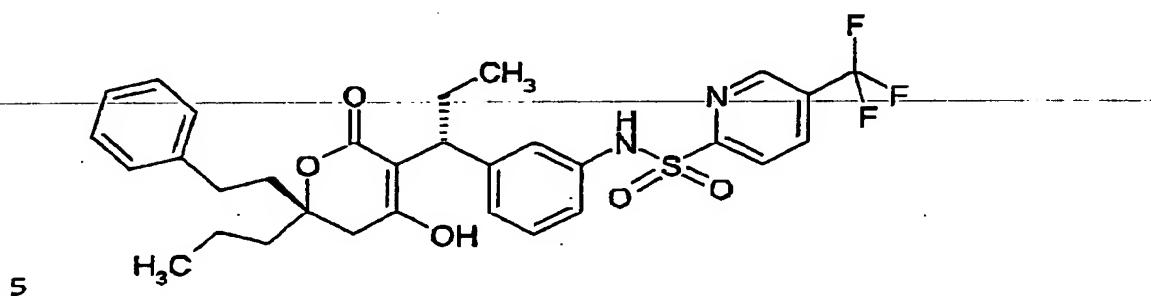
Treatment failure with rebound of the amount of HIV which can be measured in the blood is common for patients treated with combination antiretroviral regimens. Resistance to the drugs 10 in the drug regimen develops as the virus replicates in the presence of these drugs. Because of structural similarities of the drugs within an antiretroviral class, cross resistance is commonly seen to the other members of that class (for example virologic failure on a regimen containing an NNRTI will lead 15 to cross resistance to the other first generation NNRTI agents). As patients experience repeated virologic failure on antiretroviral combination therapy, their viruses develop broad multi-class antiretroviral drug resistance which limits the effectiveness of the next round of antiretroviral therapy. 20 Many highly treatment experienced patients have been exposed to all three classes of antiretroviral drugs and cannot obtain two active drugs to form the core of a new, effective antiretroviral drug regimen.

25 Tipranavir is a known agent for the treatment of HIV infection.

Tipranavir, also known as U-140690 and PNU-140690, is an HIV protease inhibitor. Chemically, tipranavir is (6R)-3-((1R)-1- 30 [3-({[5-trifluoromethyl](2-pyridyl)sulfonyl]amino}phenyl)-propyl]-4-hydroxy-6-(2-phenylethyl)-6-propyl-5,6-dihydro-2H-pyran-2-one or ([R-(R\*,R\*)]-N-[3-[1-[5,6-dihydro-4-hydroxy-2-

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oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide). It has the following structural formula:

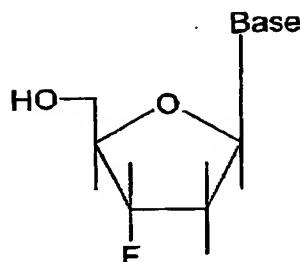


Tipranavir, and methods for its synthesis and use in the treatment of HIV are described in WO 95/30670 and corresponding U.S. Patent 5,852,195. Pharmaceutical formulations suitable for the oral administration of tipranavir are described in WO 99/06043 and WO 99/06044, and the corresponding U.S. Patents 6,121,313 and 6,231,887.

As tipranavir is metabolized relatively rapidly by the cytochromes P450, especially the Cyp3A4 isoform, it is preferred to co-administer an inhibitor of Cyp3A4 in order to obtain therapeutically effective blood levels of tipranavir. The use of ritonavir for this purpose is described in U.S. Patent 6,147,095. The use for this purpose of other inhibitors of Cyp3A4 is also possible.

Furthermore compounds of the formula (I)

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wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or 5 prodrug thereof, are described in the WO 88/00050 and WO 91/01137 for the therapeutic and prophylactic control and treatment of AIDS, HIV infections, hepatitis B virus (HBV) infections and retrovirus infections in animals and man. These nucleoside compounds are transformed by cells or enzymes to 10 triphosphates which inhibit the reverse transcriptase of retrovirus as well as the activity of DNA dependent polymerase of hepatitis B virus.

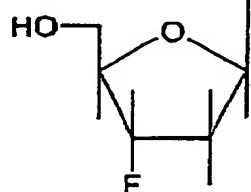
Combinations of tipranavir with at least one compound of the 15 formula (I) which exhibit potent therapeutic activity against HIV and HBV would greatly aid in the development of new combination therapy against human retroviral (HRV) infections and HBV.

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**SUMMARY OF THE INVENTION**

In one aspect, the present invention provides a novel pharmaceutical composition useful for the treatment or prophylaxis of viral infections comprising tipranavir and at least one antiviral active compound of formula (I)

Base



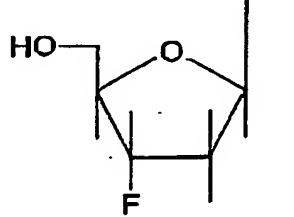
wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof.

The pharmaceutical compositions of the present invention are useful in therapy, in particular as antivirals, especially in the treatment or prophylaxis of human retroviral (HRV) infections.

In a second aspect, there is provided a use of tipranavir in combination or alternation with at least one antiviral active compound of formula (I)

20

Base



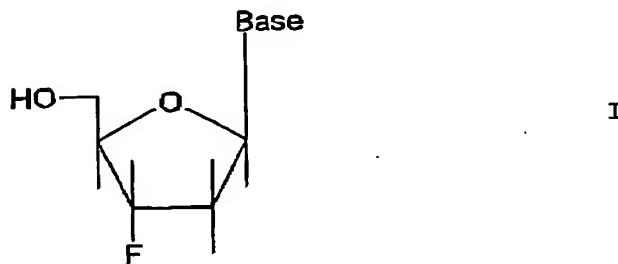
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wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, in the prophylaxis or treatment of a viral 5 infection in a patient.

In a third aspect, there is provided a use of tipranavir in combination with at least one antiviral active compound of formula (I)

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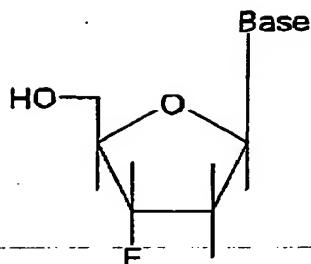


wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or 15 prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

In a fourth aspect of this invention, there is provided a kit of parts for the prophylaxis or treatment of a viral infection 20 in a patient, comprising

- (a) a first containment containing a pharmaceutical composition comprising tipranavir and at least one pharmaceutically acceptable carrier, and
- (b) a second containment containing a pharmaceutical 25 composition comprising an antiviral active compound of formula (I)

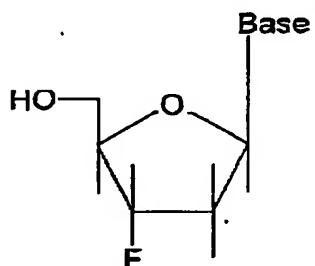
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wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 5 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier.

In a fifth aspect of this invention, there is provided a 10 manufacture comprising tipranavir and at least one antiviral active compound of formula (I)



I

wherein Base is selected from the group consisting of thymine, 15 cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

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With the combination of tipranavir and a compound of the formula (I) according to this invention, including its use in prophylaxis and treatment, the person skilled in the art can achieve an advantageous therapeutic effect to inhibit viral 5 replication, especially of human retrovirus (HRV) and HBV, in particular of multiresistant HIV. In most cases, the enhanced therapeutic effect is not attainable by administration of either agent alone. In a preferred but not necessary embodiment, the effect of administration of tipranavir and the 10 compound of formula (I) in combination or alternation is synergistic. Even though a combination exhibits additive and not synergistic effects, the combination can still provide an effect that is different from the separate administration of the two agents. For example, the biodistribution, 15 pharmacokinetics, cytotoxic effects or metabolism of one can be affected by the other.

Further aspects of the present invention become apparent to the one skilled in the art from the following detailed 20 description and examples.

#### DEFINITIONS

The term "pharmaceutically acceptable salt" means a salt of the corresponding compound which is, within the scope of sound 25 medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. 30 The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. Lists of suitable salts are found in, e.g., S.M. Birge et al.,

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J. Pharm. Sci., 1977, 66, pp. 1-19, which is hereby incorporated by reference in its entirety.

As used herein, the term "treatment" means the administration  
5 of the antivirally active compounds according to this invention in combination or alternation according to the present invention to alleviate or eliminate symptoms of the viral infection and/or to reduce viral load in a patient.

10 As used herein, the term "prevention" or "prophylaxis" means the administration of the antivirally active compounds according to this invention in combination or alternation according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms  
15 of the disease, and/or prior to the detection of the virus in the blood.

As used herein, the term "human retrovirus" (HRV) includes human immunodeficiency virus type I, human immunodeficiency  
20 virus type II, or strains thereof, as well as human T cell leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

25

#### DETAILED DESCRIPTION OF THE INVENTION

The virally active agents according to this invention may be in either free form or in protected form at one or more of the remaining (not previously protected) carboxyl, amino, hydroxy,  
30 or other reactive groups. The protecting groups may be any of those known in the art. Furthermore, the virally active agents

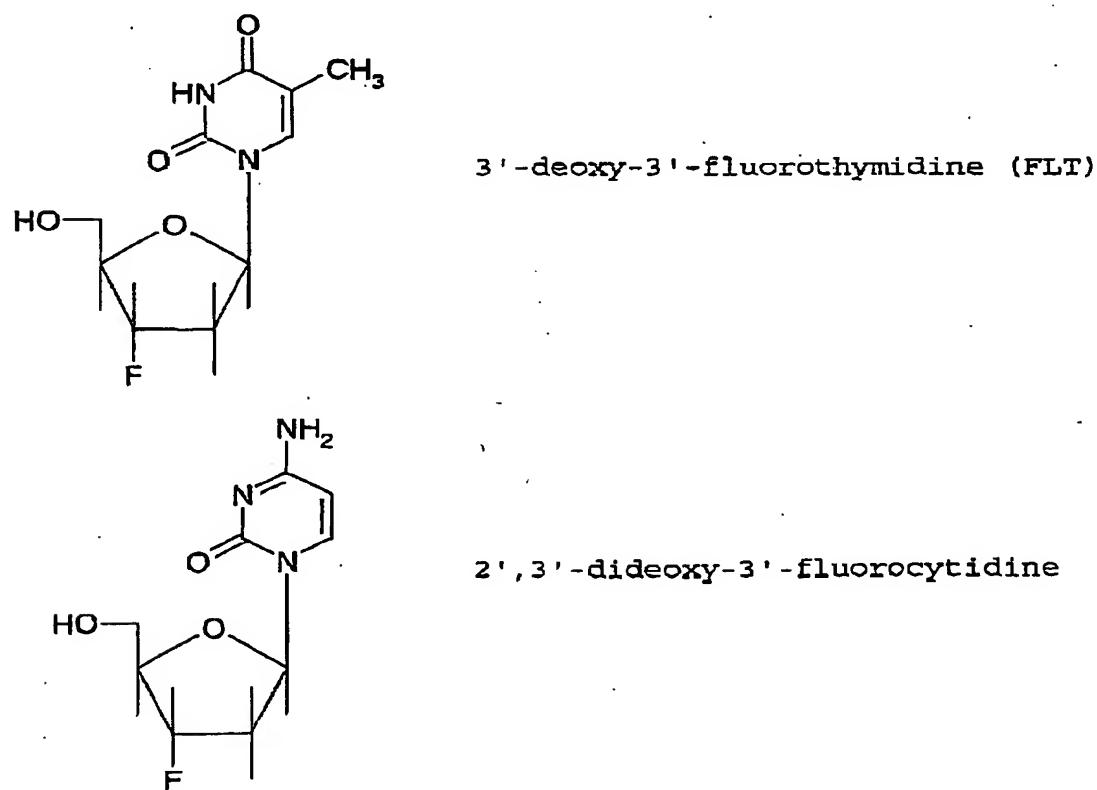
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according to this invention may also be used as in form of their pharmacologically acceptable salts and/or hydrates.

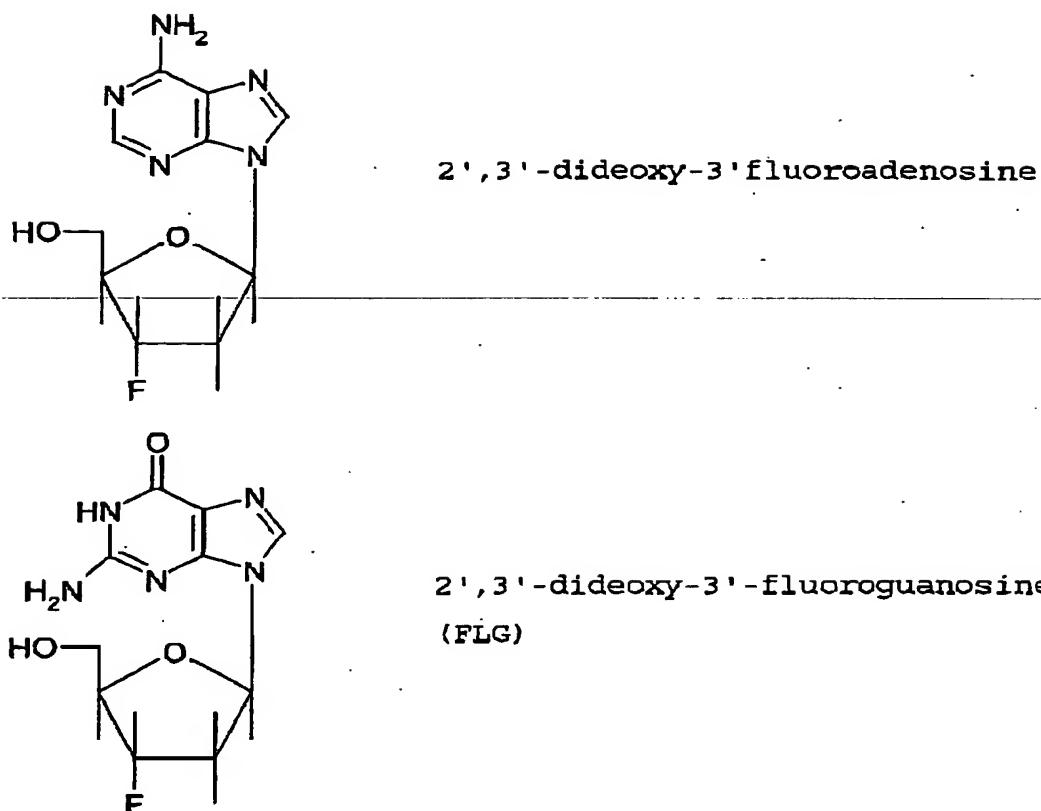
According to the first aspect of this invention, there is

5 provided a novel pharmaceutical composition useful for the treatment of viral infections comprising tipranavir and at least one antiviral active compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

10 The following known compounds constitute part of the invention as preferred compounds of the formula (I) to be combined with tipranavir:



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including pharmaceutically acceptable salts and prodrugs of the compounds listed above.

5 The most preferred compound of the formula (I) to be combined with tipranavir according to the aspects of this invention is 3'-deoxy-3'-fluorothymidine.

10 Therefore, a preferred pharmaceutical composition useful for the treatment of viral infections comprises tipranavir and 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

15 Furthermore, tipranavir in combination or alternation with preferably 3'-deoxy-3'-fluorothymidine, or a pharmaceutically

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acceptable salt or prodrug thereof, is used in the prophylaxis or treatment of a viral infection in a patient.

Also preferred is the use of tipranavir in combination with

5 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

10 A preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises

(a) a first containment containing a pharmaceutical composition comprising tipranavir and a pharmaceutically acceptable carrier, and

15 (b) a second containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

20 A preferred manufacture comprises tipranavir and 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in a patient.

25 The advantageous effects of the combination of tipranavir and the compound of formula (I) are realized over a wide ratio, like for example in a ratio of between 1:250 to 250:1.

Therefore, in the compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention, tipranavir and the at least one compound of formula (I), which is preferably 3'-deoxy-3'-fluorothymidine,

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or a pharmaceutically acceptable salt or prodrug thereof, are preferably present in a synergistic ratio. Usually, this ratio is between about 1:250 to about 250:1. More preferably the ratio is between about 1:50 to about 50:1. The most preferred 5 ratio is between about 1:20 to about 20:1, which includes the ratios 1:18, 1:16, 1:14, 1:12, 1:10, 1:8, 1:6, 1:5, 1:4, 1:3, 1:2, 5, 1:2, 1:1, 5, 1:1, 2, 1:1, 1, 2:1, 1, 5:1, 2:1, 2, 5:1, 3:1, 4:1, 5:1, 6:1, 8:1, 10:1, 12:1, 14:1, 16:1, 18:1 and all 10 ranges in between. If a further therapeutic agent is added, ratios will be adjusted accordingly.

It will be appreciated that the amount of pharmaceutical composition according to the invention required for use in treatment or prophylaxis will vary not only with the 15 particular compound selected but also with the route of administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician or 20 veterinarian. In general however the active compounds are included in the pharmaceutically acceptable carrier in an amount sufficient to deliver to a patient a therapeutically effective amount of compound to inhibit viral replication in vivo, especially HIV replication, without causing serious 25 toxic effects in the treated patient. By "inhibitory amount" is meant an amount of active ingredient sufficient to exert an inhibitory effect as measured by, for example, an assay such as the ones described herein. A suitable dose will preferably be in the range of from about 0.05 to about 200 mg/kg of body 30 weight per day.

The desired dose may conveniently be presented in a single

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dose or as divided dose administered at appropriate intervals, for example as two, three, four or more doses per day.

- 5 The pharmaceutical composition according to the present invention is conveniently administered in unit dosage form; for example containing 5 to 3000 mg, conveniently 5 to 1000 mg of active ingredient(s) per unit dosage form.
- 10 The pharmaceutical acceptable carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Examples of pharmaceutically acceptable carriers are magnesium stearate, chalk, starch, lactose, wax, gum or gelatin.
- 15 Carriers which are suited to achieve a sustained release, for example natural or synthetic polymers or liposomes, are known to the one skilled in the art. Pharmaceutically acceptable carriers also comprise liquid carriers and diluents, for example water, alcohol, glycerine or oil, which serve as a base for liquid formulations, such as solutions, suspensions or emulsions.

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- 30

The compositions referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and therefore pharmaceutical formulations comprising a composition as defined above together with a pharmaceutically acceptable carrier comprise a further aspect of the invention.

The individual components of such compositions may be

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administered either in combination, i.e. simultaneously, or in alternation, i.e. sequentially, in separate or combined pharmaceutical formulations.

5 When tipranavir is used in combination with a compound of the formula (I) against the same virus the dose of each compound may be either the same as or differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

10

The compositions according to this invention preferably also comprise at least one pharmaceutically acceptable carrier.

According to the third aspect of this invention, the  
15 combination of tipranavir and at least one compound of the formula (I) is used for the manufacture of a medicament for the prophylaxis or the treatment of a viral infection in a patient.

20 According to one embodiment, this medicament may be a unit dosage form, which is preferably useful in combination therapy, such as capsules or tablets. The unit dosage form contains a pharmaceutical composition according to this invention, i.e. tipranavir in combination with at least one  
25 compound of the formula (I), with at least one pharmaceutically acceptable carrier.

Therefore, another object of this invention also comprises bringing tipranavir and at least a compound of the formula (I) together in conjunction or association with a pharmaceutically acceptable carrier.

According to another embodiment, this medicament is a multiple dosage form, preferably a kit of parts, which is especially useful in alternation and/or combination therapy to flexibly suit the individual therapeutic needs of the patient.

5

It is known, e.g. WO 00/25784, that various doses of ritonavir have substantial and significant effects on tipranavir by elevating or enhancing plasma concentrations of tipranavir.

This pharmacokinetic drug interaction may offer the following

10 advantages:

- enhanced antiviral activity of tipranavir,
- reduction of the administered tipranavir dose,
- improved safety profile.

15 Therefore, according to one embodiment the combinations, compositions, kit of parts, manufactures of this invention and the uses thereof, which comprise tipranavir and at least one compound of the formula (I), or a pharmaceutically salt or prodrug thereof, further comprise ritonavir.

20

Following this, a preferred pharmaceutical composition useful for the treatment of viral infections comprises tipranavir in combination with ritonavir and 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

25

Furthermore, tipranavir in combination with ritonavir and in combination or alternation with preferably 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, is used in the prophylaxis or treatment of a 30 viral infection in a patient.

Also preferred is the use of tipranavir in combination with ritonavir and 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

A preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises

- (a) a first containment containing a pharmaceutical composition comprising tipranavir and ritonavir and a pharmaceutically acceptable carrier, and
- (b) a second containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

Another preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises

- (a) a first containment containing a pharmaceutical composition comprising tipranavir and a pharmaceutically acceptable carrier, and
- (b) a second containment containing a pharmaceutical composition comprising ritonavir and a pharmaceutically acceptable carrier, and
- (c) a third containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

- A preferred manufacture comprises tipranavir, ritonavir and 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, for use in combination or alternation

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in the prophylaxis or treatment of a viral infection in a patient.

In said combinations, compositions, kit of parts, manufactures, which comprise tipranavir, ritonavir and at least one compound of the formula (I); preferably 3'-deoxy-3'-fluorothymidine, or a pharmaceutically salt or prodrug thereof, the ratio and the amount of tipranavir and ritonavir present in these combinations are preferably chosen to achieve therapeutically effective plasma levels of tipranavir. Upper limits, lower limits and therapeutically preferred areas of dosage regimens are known from scientific literature, e.g. WO 00/25784, and may be optimized in view of the combination with the compounds of the formula (I) according to known methods.

According to a further embodiment the combinations, compositions, kit of parts, manufactures of this invention and the uses thereof, which comprise tipranavir and at least one compound of the formula (I), or a pharmaceutically salt or prodrug thereof, further comprise a further nucleoside reverse transcriptase inhibitor (NRTI), preferably other than 3'-deoxy-3'-fluorothymidine.

Following this, a preferred pharmaceutical composition useful for the treatment of viral infections comprises tipranavir in combination with 3'-deoxy-3'-fluorothymidine and a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

Furthermore, tipranavir in combination or alternation with preferably 3'-deoxy-3'-fluorothymidine and a further NRTI, or

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a pharmaceutically acceptable salt or prodrug thereof, is used in the prophylaxis or treatment of a viral infection in a patient.

5 Also preferred is the use of tipranavir in combination with 3'-deoxy-3'-fluorothymidine and a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

10

A preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises

(a) a first containment containing a pharmaceutical composition comprising tipranavir and a pharmaceutically acceptable carrier; and

(b) a second containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine and a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

20

Another preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises

(a) a first containment containing a pharmaceutical composition comprising tipranavir and a pharmaceutically acceptable carrier; and

(b) a second containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier; and

30 (c) a third containment containing a pharmaceutical composition comprising a further NRTI, or a pharmaceutically

acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

A preferred manufacture comprises tipranavir, 3'-deoxy-3'-fluorothymidine and a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof; for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

10 In said combinations, compositions, kit of parts, manufactures and uses thereof, which additionally comprise a further NRTI, tipranavir may advantageously be combined with ritonavir as described hereinbefore.

15 In the foregoing and in the following, the term "a further NRTI" refers to a nucleoside reverse transcriptase inhibitor, or a pharmaceutically acceptable salt or prodrug thereof, preferably other than 3'-deoxy-3'-fluorothymidine. Examples of further NRTIs are AZT, ddi, d4T, ddc, 3TC, FLG, Abacavir, Emtricitabine, Amdoxovir/DAPD, Ach-126443 and including those NRTIs listed hereinafter. Preferred further NRTI are selected from the group consisting of AZT, ddi, 3TC, ddc, d4T and FLG, including its prodrugs. Especially preferred as a further NRTI is FLG and its prodrugs, in particular those described in WO 25 99/09031 and WO 99/41268, which documents in their entirety are incorporated herein by reference.

In a still further embodiment, the pharmaceutical compositions of the present invention may comprise at least one further 30 antiviral agent. The further antiviral agent is preferably chosen from the group consisting of NRTIs (nucleoside-analogue

reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors) and protease inhibitors.

Examples of further antiviral agents are 3TC (lamivudine), AZT

5 (zidovudine), FTC (5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine), d4T (2',3'-dideoxy-2',3'-didehydro-thymidine, stavudine and Zerit), nevirapine, DMP-226, nevirapine, delavirdine, 19-[(2-hydroxymethyl)-1,3-dioxolan-4-yl]guanine, 2-amino-9-[(2-hydroxymethyl)-1,3-dioxolan-4-

10 yl]adenine, MKC-442, 1592U89 (abacavir), 141W94, MK-639, EMS-234475, PNU-140690, ABT-378, DMP-450, Indinavir, saquinavir, ritonavir, efavirenz (sustiva), TIBO, HEPT, BHAP, a-APA, TSAO, calanolides, L-697,661, 2',3'-dideoxycytidine (ddC or

zalcitabine), 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine

15 (ddI or didanosine), 3'-deoxythymidine, 2',3'-dideoxy-2',3'-didehydrocytidine, ribavirin, DMP-450 (Triangle Pharmaceuticals, Inc.), 141W94 (amprenavir, GlaxoWellcome, Inc.), Rescriptor (delavirdine), abacavir (1592U89), carbovir, CS-92 (3'-azido-2',3'-dideoxy-5-methyl-cytidine), b-D-

20 dioxolane nucleosides such as b-D-dioxolanylguanine (DXG), b-D-dioxolanyl-2,6-diaminopurine (DAPD), and b-D-dioxolanyl chloropurine (ACP); acyclic nucleosides such as acyclovir, ganciclovir; interferons such as alpha-, beta- and gamma-interferon; glucuronation inhibitors such as probenecid;

25 nucleoside transport inhibitors such as dipyridamole; immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, ampligen, thymomodulin, thymopentin, foscarnet, glycosylation inhibitors such as 2-deoxy-D-glucose, castanospermine, 1-deoxynojirimycin; and inhibitors of HIV binding to CD4 receptors such as soluble CD4, CD4 fragments, CD4-hybrid

22

molecules and inhibitors of the HIV aspartyl-protease such as L-735,524.

The further antiviral agent is preferably chosen from  
5 zidovudine, didanosine, zalcitabine, stavudine, lamivudine, nevirapine, delavirdine, efavirenz, indinavir, nelfinavir and  
saquinavir.

The compounds, or their pharmaceutically acceptable derivative  
10 or salts thereof, can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, antiinflammatories, protease inhibitors, or other nucleoside or non-nucleoside antiviral  
15 agents, as discussed in more detail above.

In general, during alternation therapy, an effective dosage of each agent is administered serially, whereas in combination therapy, an effective dosage of two or more agents are  
20 administered together. The dosages will depend on such factors as absorption, biodistribution, metabolism and excretion rates for each drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It  
25 is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Examples of suitable  
30 dosage ranges for tipranavir, compounds of formula (I), preferably 3'-deoxy-3'-fluorothymidine, ritonavir, further NRTIs and other antivirals can be found in the scientific

literature. Many examples of suitable dosage ranges for other compounds described herein are also found in the public literature or can be identified using known procedures. These dosage ranges can be modified as desired to achieve a desired 5 result.

It has been recognized that drug-resistant variants of HIV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that 10 encodes for an enzyme used in the viral life cycle, and most typically in the case of HIV, in either the reverse transcriptase or protease genes. It has been demonstrated that the efficacy of a drug against HIV infection can be prolonged, augmented, or restored by administering the compound in 15 combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation(s) from that selected for by the principle drug. Alternatively, the pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation 20 therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus. In the case of administering the antiviral compounds in alternation, i.e. sequentially, the time gap between administering the first 25 compound and the second compound is preferably not too long in order to achieve a beneficial effect. Preferably, the time gap is less than half a day, most preferably less than 6 hours.

While it is possible that, for use in therapy, a compound 30 of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation. The invention thus further

provides a pharmaceutical formulation comprising tipranavir and a compound of the formula (I) with one or more pharmaceutically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients.

5

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-  
lingual), transdermal, vaginal or parenteral (including  
intramuscular, sub-cutaneous and intravenous) administration.

10 in liquid or solid form or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of  
15 bringing into association the active compound(s) with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

20 Pharmaceutical formulation suitable for oral administration may conveniently be presented as discrete units such as capsules, including soft gelatin capsules, cachets or tablets, each containing a predetermined amount of the active ingredient(s); as a powder or granules; as a solution, a  
25 suspension or as an emulsion, for example as syrups, elixirs or self-emulsifying delivery systems (SEDDS). The active ingredient(s) may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for

example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

~~The pharmaceutical composition according to the invention may also be formulated for parenteral administration (e.g.~~

10 by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, 15 solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient(s) may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation 20 from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

~~Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most 25 preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound(s) with the softened or melted carrier(s) followed by chilling and 30 shaping in moulds.~~

When desired the above described formulations adapted to

give sustained release of the active ingredient(s) may be employed.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention are advantageous in the treatment and/or prophylaxis of viral infections in a patient, preferably human retrovirus (HRV) infections and hepatitis B, in particular HIV infections, especially multiresistant HIV infections. Therefore this invention may offer an aid especially for highly treatment experienced patients suffering from multiresistant HIV. In addition to the treatment of said diseases, the combinations, formulations and compositions according to this invention can be used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-HIV antibody or HIV-antigen positive or who have been exposed to HIV.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention may also be beneficial in preventing perinatal transmission of human retroviral (HRV) infections, in particular HIV-1, from mother to baby. According to this method, tipranavir and a compound of the formula (I), preferably 3'-deoxy-3'-fluorothymidine, and optionally further active compounds as described hereinbefore or hereinafter are administered in combination or alternation to the mother before giving birth.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention may also be beneficial in the treatment and/or prophylaxis of other HIV/AIDS-related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-

related neurological conditions, anti-HIV antibody positive and HIV-positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections.

5 Therefore, patients to be treated would be especially those individuals:

1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum, and/or

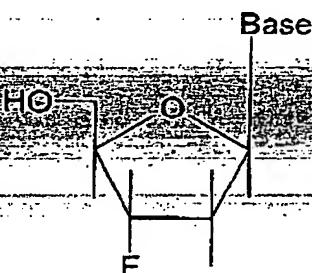
10 2) in the case of HIV, having either a asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isopsoriasis, iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia; iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/mm<sup>3</sup> in the peripheral blood.

The pharmaceutical combination according to this invention can be tested for additive and synergistic activity against HIV according to a number of assays known in scientific and public literature, including the one described in the WO 98/44913 and WO 00/51641, which are included herein by way of reference.

**Claims:**

1. A pharmaceutical composition useful for the treatment or prophylaxis of viral infections comprising tipranavir and at least one antiviral active compound of formula (I).

5



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof.

10 prodrug thereof.

2. The pharmaceutical composition according to claim 1 wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

3. The pharmaceutical composition according to one or more of the claims 1 to 2 wherein tipranavir and the at least one compound of formula (I) are present in a synergistic ratio.

20

4. The pharmaceutical composition according to one or more of the claims 1 to 3 wherein tipranavir and the at least one compound of the formula (I) are present in a ratio between about 1:250 to about 250:1.

25

29

5. The pharmaceutical composition according to claim 4 wherein tipranavir and the at least one compound of the formula (I) are present in a ratio between about 1:50 to about 50:1.

5 6. The pharmaceutical composition according to one or more of the claims 1 to 5 further comprising ritonavir.

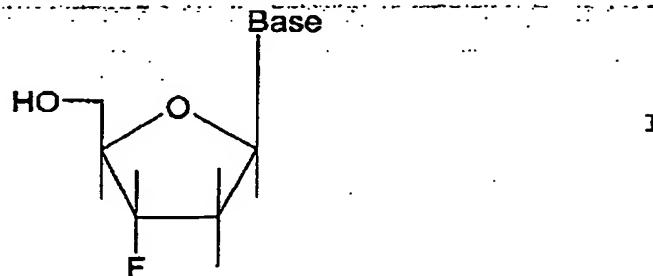
~~7. The pharmaceutical composition according to one or more of the claims 1 to 6 further comprising a further NRTI, or a 10 pharmaceutically acceptable salt or prodrug thereof.~~

8. The pharmaceutical composition according to one or more of the claims 1 to 7 with at least one pharmaceutically acceptable carrier.

15

9. The pharmaceutical composition according to one or more of the claims 1 to 8 for use in the treatment or prophylaxis of human retroviral (HRV) infections.

20 10. Use of tipranavir in combination or alternation with at least one antiviral active compound of formula (I)



25 wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or

prodrug thereof, in the prophylaxis or treatment of a viral infection in a patient.

11. The use according to claim 10, wherein the compound of  
5 formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

~~12. The use according to claim 10 or 11 in the prophylaxis or treatment of a human retroviral infection (HRV) in a patient.~~

10

13. The use according to claim 10 or 12 in the prophylaxis or treatment of a multiresistant HIV infection in a patient.

14. The use according to one or more of the claims 10 to 13  
15 for preventing perinatal transmission of a human retroviral (HRV) infection from mother to baby.

16. The use according to one or more of the claims 10 to 14, wherein tipranavir and the at least one compound of formula  
20 (I) are administered to the patient in combination or alternation in a synergistic ratio.

17. The use according to one or more of the claims 10 to 15, wherein tipranavir and the at least one compound of formula  
25 (I) are administered to the patient in combination or alternation in a ratio between about 1:250 to about 250:1.

18. The use according to claim 16, wherein tipranavir and the at least one compound of formula (I) are administered to the  
30 patient in combination or alternation in a ratio between about 1:50 to about 50:1.

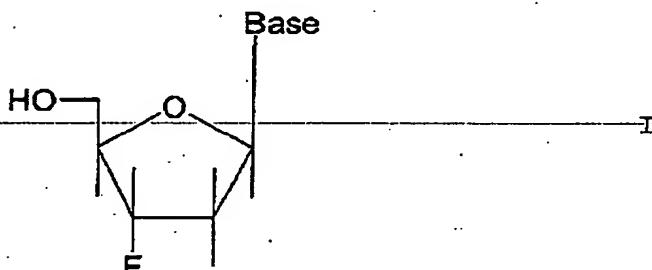
- 31 -

18. The use according to one or more of the claims 10 to 17, wherein tipranavir is used in combination with ritonavir and in combination or alternation with said compound of the formula (I).

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19. The use according to one or more of the claims 10 to 18 in combination or alternation with a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

10 20. Use of tipranavir in combination with at least one antiviral active compound of formula (I)



wherein Base is selected from the group consisting of thymine, 15 cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2',6'-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

20 21. The use according to claim 20, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

25

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22. The use according to claim 20 or 21, wherein tipranavir is used in combination with ritonavir and said compound of the formula (I).

5 23. The use according to one or more of the claims 20 to 22, wherein tipranavir is used in combination with said compound of the formula (I) and a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

10 24. The use according to one or more of the claims 20 to 23 for the manufacture of a medicament for the prophylaxis or treatment of a human retroviral (HRV) infection in a patient.

25. The use according to one or more of the claims 20 to 24, wherein the medicament is a single dosage form.

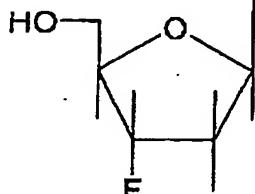
26. The use according to one or more of the claim 20 to 25, wherein the medicament is a multiple dosage form.

20 27. A kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprising

(a) a first containment containing a pharmaceutical composition comprising tipranavir and at least one pharmaceutically acceptable carrier, and

25 (b) a second containment containing a pharmaceutical composition comprising an antiviral active compound of formula (I)

## Base



I

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or

5 prodrug thereof, and at least one pharmaceutically acceptable carrier.

28. The kit of parts according to claim 27, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a  
10 pharmaceutically acceptable salt or prodrug thereof.

29. The kit of parts according to claim 27 or 28 for use in the prophylaxis or treatment of a human retroviral (HRV) infection in a patient.

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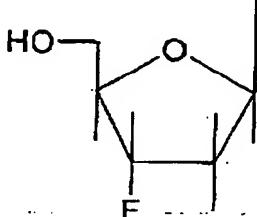
30. The kit of parts according to one or more of the claim 27 to 29 further comprising ritonavir.

31. The kit of parts according to one or more of the claim 27 to 30 further comprising a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

32. A manufacture comprising tipranavir and at least one antiviral active compound of formula (I)

25

Base



I

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or

5 prodrug thereof; for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

33. The manufacture according to claim 32, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a 10 pharmaceutically acceptable salt or prodrug thereof.

34. The manufacture according to claim 32 or 33, for use in combination or alternation in the prophylaxis or treatment of a human retroviral (HRV) infection in patient.

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35. The manufacture according to one or more of the claims 32 to 34 further comprising ritonavir.

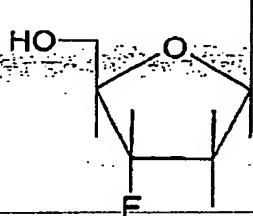
36. The manufacture according to one or more of the claims 32 20 to 35 further comprising a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

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### Summary

5 In accordance with the present invention there is provided a pharmaceutical composition useful for the treatment or prophylaxis of viral infections comprising tipranavir and at least one antiviral active compound of formula (I)

Base



10

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof.

